Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 25-27, 46, 55, 57-59 and 61-74 are pending in the application, with claims 27, 46 and 58 being the independent claims. Claims 27, 46 and 58 have been amended.

Claim 46 has been amended to explicitly state that groups G and D encompasses the N-oxides of nitrogen containing heteroaryl groups. Support for this amendment can be found at page 62, line 5, of the application as filed. In claim 46, the definition of $-C(O)-CH_2-Y-G$ has been limited by amending the relevant proviso so that when R_3 is $-C(O)-CH_2-Y-G$ and G is C-attached heteroaryl, then R_1 is other than hydrogen, alkyl, haloalkyl, alkenyl or alkynyl.

Claim 46 has also been amended by limiting the definitions of groups D and E. Group D is now defined as "C-attached heteroaryl, or a quaternary ammonium salt or N-oxide of a nitrogen containing heteroaryl group." Group E has been deleted from the claim. Claim 27, claim 58, and the provisos to claim 46 have been amended to conform with the amended definitions of groups G, D and E.

Claims 68-74 are sought to be added. Support for new claims 68-70 can be found, *inter alia*, at page 17, lines 18-19, and in claims 1 and 3, of the application as filed. Support for new claim 73 can be found, *inter alia*, at page 26, lines 29-30, and in claim 27 of the application as filed.

The proposed amendments to the claims are necessary in order to more clearly define the scope of the invention. They were not made earlier because Applicants' believe that the claims as previously amended are patentably distinct from the disclosure of WO 94/27608 (Gee *et al.*)

and U.S. Patent No. 5,232,917 (Bolger *et al.*). The proposed amendments further distinguish the cited documents.

The present amendments place the application in better form for appeal by materially simplifying the issues for appeal. These amendments would not require further consideration or search, as they do not add new subject matter.

I. First Rejection Under 35 U.S.C. § 103(a)

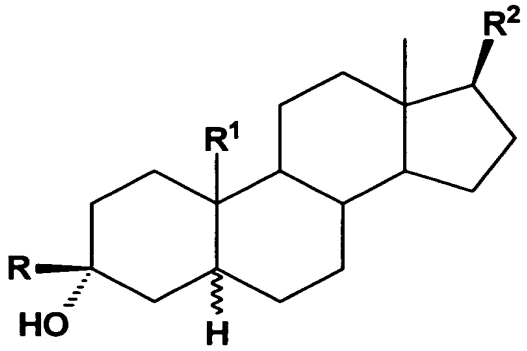
In the previous Office Action (File Wrapper Paper No. 13), the Examiner rejected claims 25-27, 46, 55, 57, 59 and 62 under 35 U.S.C. § 103(a) as obvious in view of Gee *et al.* (WO 94/27608). In this Final Office Action (File Wrapper Paper No. 15), the Examiner has maintained this rejection.

Specifically, the Examiner is of the opinion that:

> The reference teaches R can be hydrogen, alkyl, alkynyl, trihaloalkyl, monohaloalkyl, alkenyl and aralkyl (see page 11, lines 9-15). The reference also teaches that "[a] preferred group of compounds include those in which **R is not hydrogen** . . ." (see page 12, lines 5-6). Another preferred group of compounds are those cited by applicant. It is noted, however, that said group does not include compounds wherein R is hydrogen. According to page 12, lines 14-16, R is lower alkyl or trihalo(lower)alkyl. Even if one agrees that R is hydrogen in said group, the preceding paragraph and the first two paragraphs on page 13 teach R is preferably not hydrogen. Therefore, the reference provides sufficient guidance/direction to modify the exemplified compounds, including 3α-hydroxy-21(pyrid-4-ylthio)-5β-pregnan-20-one, making compounds wherein R is not hydrogen but groups such as lower alkynyl or trihalo(lower)alkyl groups as recited by the instant claims.

(Office Action, File Wrapper Paper No. 15, section 3, lines 1-18). Applicants respectfully traverse this continued rejection.

Gee *et al.* disclose 3α-hydroxy pregnanes of the following formula I:



(I)

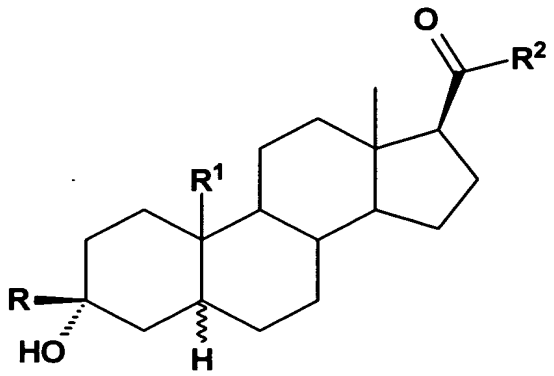
wherein:

R, the 3β-position, is hydrogen, a lower alkyl group, e.g., methyl and methoxymethyl, a lower alkynyl group, e.g., ethynyl, 4-hydroxypent-1-ynyl and (4'-acetylphenyl)ethynyl, a lower trihaloalkyl group, e.g., trifluoromethyl, a lower monohaloalkyl group, e.g., chloromethyl, a lower alkenyl group, e.g., ethenyl and 2-phenylethenyl, an aryl group, e.g., phenyl, or an aralkyl group, e.g., benzyl; and

R^2, the 17β-position, pyrid-4-ylthioacetyl, ethylene, propylene, 2'-hydroxyacetyl hemisuccinate sodium salt, 1-hydroxybutyl, 1-hydroxy-1-methylethyl, 1-hydroxypropyl, 1-propionyl, 3-methoxypropionyl, ethynyl, 2'-mesyloxyacetyl, or 1'-(ethylenedioxy)ethyl.

The pyrid-4-ylthioacetyl group recited above for R^2 appears to be the only group including a heteroaryl group.

On page 12, lines 9-25, Gee *et al.* describe a preferred group of compounds of the following formula II:



(II)

wherein:

R, the 3β-position, is a lower alkyl group, e.g., methyl, a lower alkynyl group, e.g., ethynyl, or a trihalo(lower) alkyl group, e.g., trifluoromethyl; and

R^2, the 21-position, is hydrogen, hydroxy, a pyrid-4-ylthio group, a hemisuccinoyloxy group, or a phosphoryloxy group and the sodium salts thereof, subject to three provisos.

In contrast to the compounds disclosed in Gee *et al.*, the compounds claimed in the present application do not include compounds which are substituted in the 17β-position by a pyrid-4-ylthioacetyl group or a pyrid-4-ylthiocarbonyl group when the 3β-position is substituted by hydrogen, alkyl, haloalkyl, alkenyl or alkynyl. Therefore, claims 25-27, 46, 55, 57, 59 and 62 are not obvious in view of Gee *et al.* Gee *et al.* does not teach or suggest the groups required by the pending claims. Applicants respectfully submit that this objection under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

II. Second Rejection Under 35 U.S.C. § 103(a)

In the previous Office Action (File Wrapper Paper No. 13), the Examiner rejected claims 25-27, 46, 55, 57-59, 61 and 64-65 under 35 U.S.C. § 103(a) as obvious in view of Bolger *et al.* (U.S. Patent No. 5,232,917). In this Final Office Action (File Wrapper Paper No. 15), the Examiner has maintained this rejection.

Specifically, the Examiner is of the opinion that:

> Applicant argument is based on the decision make in *In re Baird*. According to applicant none of the exemplified prior art compounds have the 17β-C(O)-CH_2-O-R16 as claimed by the present invention. Applicant's argument was considered but not persuasive for the following reasons.
>
> Unlike, *In re Baird*, the claimed invention, like the prior art, is drawn to a vast number of compounds and, thus, the decision of Baird does not apply. One has to look at the prior art as a whole and what it teaches the ordinary artisan. The reference teaches and exemplifies compounds having 17β-C(O)-CH_2-O-C(O)R16 and an equivalence between O-C(O)R16 and O-R16. The reference also teaches an equivalence between alkyl, aryl and heterocyclic groups. Thus, the modification of the exemplified compounds having 17β-C(O)-CH_2-O-C(O)R16 with a group having 17β-C(O)-CH_2-O-R16 wherein R16 is aryl or a heterocyclic group is prima facie obvious.

(Office Action, File Wrapper Paper No. 15, section 4, lines 1-14). Applicants respectfully traverse this rejection.

Applicants' claims, as amended, do not encompass compounds wherein the substituent at the 17β-position is -C(O)-CH_2-O-E, and E is an optionally substituted aryl group. Applicants respectfully request that the Examiner reconsider the arguments that were submitted in Applicant's Amendment and Reply that was filed on February 28, 2001, which is entirely incorporated by reference herein. Bolger *et al.* do not exemplify any compounds wherein the C-21 position is substituted by either aryloxy or heteroaryloxy (*see* Examples 1-30 and Tables 2 and 3). Therefore, claims 25-27, 46, 55, 57-59, 61 and 64-65 are not obvious in view of Bolger *et al.* Bolger *et al.* does not teach or suggest the groups required by the pending claims.

Applicants respectfully submit that this rejection under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Applicants note that the subject matter of pending claims 63, 66 and 67 and the subject matter of new claims 68 and 69 does not fall within the scope of the rejections that have been made by the Examiner in this Final Office Action.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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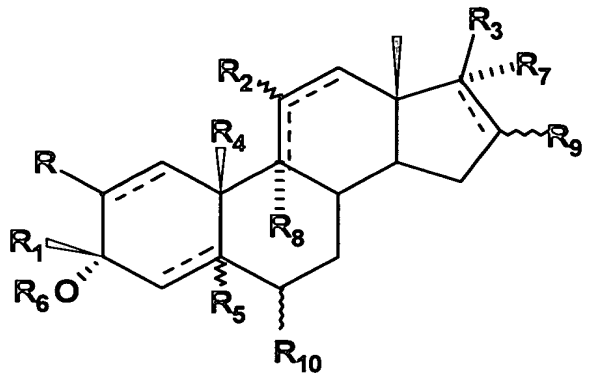
Version with markings to show changes made

In the Claims:

Claims 27 and 46 has been amended as follows:

27. (thrice amended) A compound selected from the group consisting of [3α-hydroxy-3β-(4-hydroxybutynyl)-21-(pyrid-4-ylthio)-5β-pregnan-20-one; 3α-hydroxy-21-(pyrid-4-yloxy)-5β-pregnan-20-one;] 3α-hydroxy-2β-propoxy-21-(pyrid-4-ylthio)-5α-pregnan-20-one N-methyl iodide; 3α-hydroxy-21-(pyrid-4-ylthio)-5α-pregnan-20-one N-methyl iodide; 3α-hydroxy-21-(pyrid-4-yl)thio-5β-pregnan-20-one N-methyl iodide; 3α-hydroxy-3β-methoxymethyl-21-(pyrid-4-ylthio)-5α-pregnan-20-one; [21-(4′-dimethylaminophenylthio)-3α-hydroxy-3β-methoxymethyl-5α-pregnan-20-one; 3α-hydroxy-3β-methoxymethyl-21-(4′-nitrophenylthio)-5α-pregnan-20-one; 3α-hydroxy-3β-methoxymethyl-21-(4′-nitrophenylsulfinyl)-5α-pregnan-20-one; 3α-hydroxy-3β-methoxymethyl-21-(4′-nitrophenylsulfonyl)-5α-pregnan-20-one; 21-(4′-dimethylaminophenoxy)-3α-hydroxy-3β-methyl-5α-pregnan-20-one; 3α-hydroxy-3β-methyl-21-(4′-nitrophenoxy)-5α-pregnan-20-one; 3α-hydroxy-3β-methyl-21-(4′-trimethylammoniumphenoxy)-5α-pregnan-20-one iodide salt; 21-(4′-fluorophenylthio)-3α-hydroxy-3β-methoxymethyl-5α-pregnan-20-one; 3β-ethynyl-3α-hydroxy-21-(pyrid-4-ylthio)-5α-pregnan-20-one;] 3β-(4′-acetylphenyl)ethynyl-3α-hydroxy-21-(pyrid-4-ylthio)-5β-pregnan-20-one; [3α-hydroxy-2β-propoxy-21-(-4′-N,N,N-trimethylammoniumphenoxy)-5α-pregnan-20-one iodide salt;] 3α-hydroxy-3β-methyl-21-(quinolin-6-yloxy)-5α-pregnan-20-one N-methyl iodide; and 3α-hydroxy-3β-methyl-21-(quinolin-6-yloxy)-5α-pregnan-20-one[; 21-(4′fluorophenyl)sulfonyl-3α-hydroxy-3β-methoxymethyl-5α-pregnan-20-one; 3α-hydroxy-3β-methoxymethyl-21-(4′-pyrrolidinophenyl)sulfonyl-5α-pregnan-20-one and 21-(4′-aminophenylthio)-3α-hydroxy-3β-methoxymethyl-5α-pregnan-20-one].

46. (thrice amended) A compound of the formula:



or a physiologically acceptable salt or 3-ester thereof; wherein

R is one of hydrogen, amino, thio, sulfinyl, sulfonyl, halogen, lower alkoxy, alkynyl or substituted alkynyl;

R_1 is one of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, dihaloalkyl, trihaloalkyl, optionally substituted aralkynyl, alkoxyalkyl, aminoalkyl, cyano, cyanoalkyl, thiocyanoalkyl, azidoalkyl, optionally substituted arylalkyl, arylalkenyl, optionally substituted aryl, optionally substituted aralkylalkynyl, alkanoyloxyalkynyl, optionally substituted heteroaryloxyalkynyl, oxoalkynyl or a ketal thereof, cyanoalkynyl, optionally substituted heteroarylalkynyl, hydroxyalkynyl, alkoxyalkynyl, aminoalkynyl, acylaminoalkynyl, mercaptoalkynyl, hydroxyalkynyl dioic acid hemi-ester or a salt thereof, or alkynyloxyalkynyl;

R_2 is one of hydrogen, alkoxy, a keto group or a dimethylamino group;

R_3 is one of -C(O)-CH_2-Y-G, -C(O)-CH_2-O-D, [-C(O)-CH_2-O-E,] -C(O)-CH_2-Z-G, or -C(O)-CH_2-Y′-Z-G;

Y is one of S, SO or SO_2;

Y′ is one of O, S, SO or SO_2;

Z is one of alkylene, alkenylene or alkynylene;

G is one of C-attached heteroaryl, [optionally substituted aryl,] or a quaternary ammonium salt or N-oxide of a nitrogen containing heteroaryl group [or a quaternary ammonium salt of an amino substituted aryl group];

D is C-attached heteroaryl, or a quaternary ammonium salt or N-oxide of a nitrogen containing heteroaryl group;

[E is optionally substituted aryl or a quaternary ammonium salt of an amino substituted aryl group;]

R_4 is one of hydrogen or methyl;

R_5, R_6, R_7, R_8, R_9 and R_{10} are each hydrogen; and

the dotted lines all represent single bonds; with the following provisos:

when R_3 is -C(O)-CH_2-Y-G, and G is C-attached [heteroaryl] pyridyl [or optionally substituted aryl,] then R_1 is other than hydrogen [or], alkyl, haloalkyl, alkenyl or alkenyl;

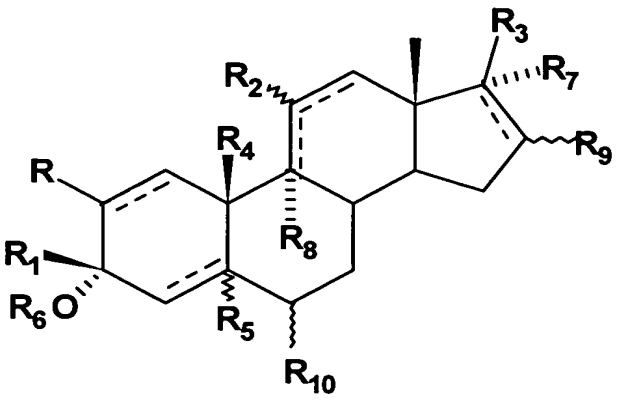
[when R_3 is -C(O)-CH_2-O-E, and E is optionally substituted aryl, then R_1 is other than hydrogen or alkyl;

when R_3 is -C(O)-CH_2-Y′-Z-G, and Y′ is O, and G is aryl, then R_1 is other than hydrogen or alkyl;

when R_3 is -C(O)-CH_2-Y′-Z-G, and Y′ is S, SO, or SO_2, and G is aryl, then R_1 is other than hydrogen or alkyl;] and

when R_3 is -C(O)-CH_2-Z-G, then R_1 is other than hydrogen.

58. (twice amended) A compound of the formula:



or a physiologically acceptable salt or 3-ester thereof; wherein

R is one of hydrogen, amino, thio, sulfinyl, sulfonyl, halogen, lower alkoxy, alkynyl or substituted alkynyl;

R_1 is one of hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, dihaloalkyl, trihaloalkyl, optionally substituted aralkynyl, alkoxyalkyl, aminoalkyl, cyano, cyanoalkyl, thiocyanoalkyl, azidoalkyl, optionally substituted arylalkyl, arylalkenyl, optionally substituted aryl, optionally substituted aralkylalkynyl, alkanoyloxyalkynyl, optionally substituted heteroaryloxyalkynyl, oxoalkynyl or a ketal thereof, cyanoalkynyl, optionally substituted heteroarylalkynyl, hydroxyalkynyl, alkoxyalkynyl, aminoalkynyl, acylaminoalkynyl, mercaptoalkynyl, hydroxyalkynyl dioic acid hemi-ester or a salt thereof, or alkynyloxyalkynyl;

R_2 is one of hydrogen, alkoxy, a keto group or a dimethylamino group;

R_3 is [-$C(O)CH_2S$-(4-fluorophenyl),] -$C(O)CH_2O$-(6-quinolinyl), [-$C(O)CH_2SO_2$-(4-fluorophenyl),] -$C(O)CH_2SO_2$-(4-pyrrolidinophenyl), or -$C(O)CH_2CH_2$-(4-pyridyl), [-$C(O)CH_2O$-(4-nitrophenyl), -$C(O)CH_2O$-(4-dimethylaminophenyl), -$C(O)CH_2SO$-(4-nitrophenyl) or -$C(O)CH_2SO_2$-(4-nitrophenyl)];

R_4 is one of hydrogen or methyl;

R_5, R_6, R_7, R_8, R_9 and R_{10} are each hydrogen; and

the dotted lines all represent single bonds; with the following provisos:

when R_3 is [-C(O)CH_2S-(4-fluorophenyl), -C(O)CH_2SO_2-(4-fluorophenyl),] -C(O)CH_2SO_2-(4-pyrrolidinophenyl), [-C(O)CH_2SO-(4-nitrophenyl) or -C(O)CH_2SO_2-(4-nitrophenyl),] then R_1 is other than hydrogen or alkyl; and

when R_3 is [-C(O)CH_2O-(4-nitrophenyl), -C(O)CH_2O-(4-dimethylaminophenyl) or] -C(O)CH_2CH_2-(4-pyridyl), then R_1 is other than hydrogen [or], alkyl, haloalkyl, alkenyl or alkenyl.

Claims 68-74 have been added.